A Slow Starvation:
Adjuvant Endocrine Therapy of Breast Cancer

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Surgical Oncology Update
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Disclosure slide

- Participant in various meetings or advisory boards sponsored by Novartis and Pfizer
- Honoraria deposited to education account for clinical trials staff at BCCA-SI
- CSI has received some funding for breast education initiatives from AstraZeneca

Adjuvant hormone therapy: a long slow siege

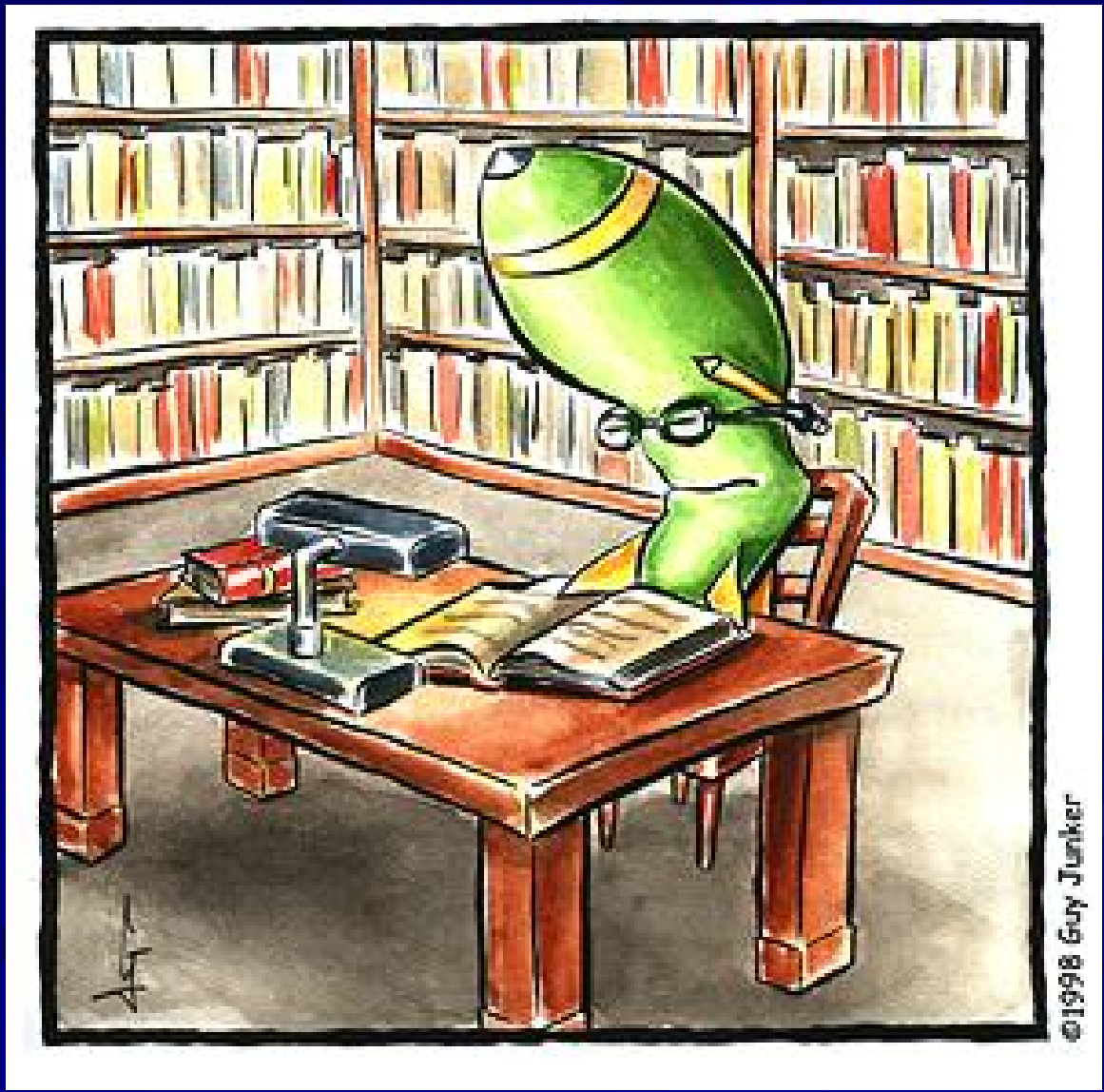
Adjuvant chemotherapy: short, nasty and brutish

“siege”

- **a military blockade of a city or fortified place to compel it to surrender**
- **a persistent or serious attack**

- lay siege to
  - 1 : **to besiege militarily**
    2 : **to pursue diligently or persistently**

Targeted biologic therapy?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Outline

- The big picture

- Endocrine therapy then and now…
- Just why are we doing this?
- Something for everyone?
- Who gets what why?
- Surgical precision: nodes, DCIS
- Where are we going from here?

- Summary

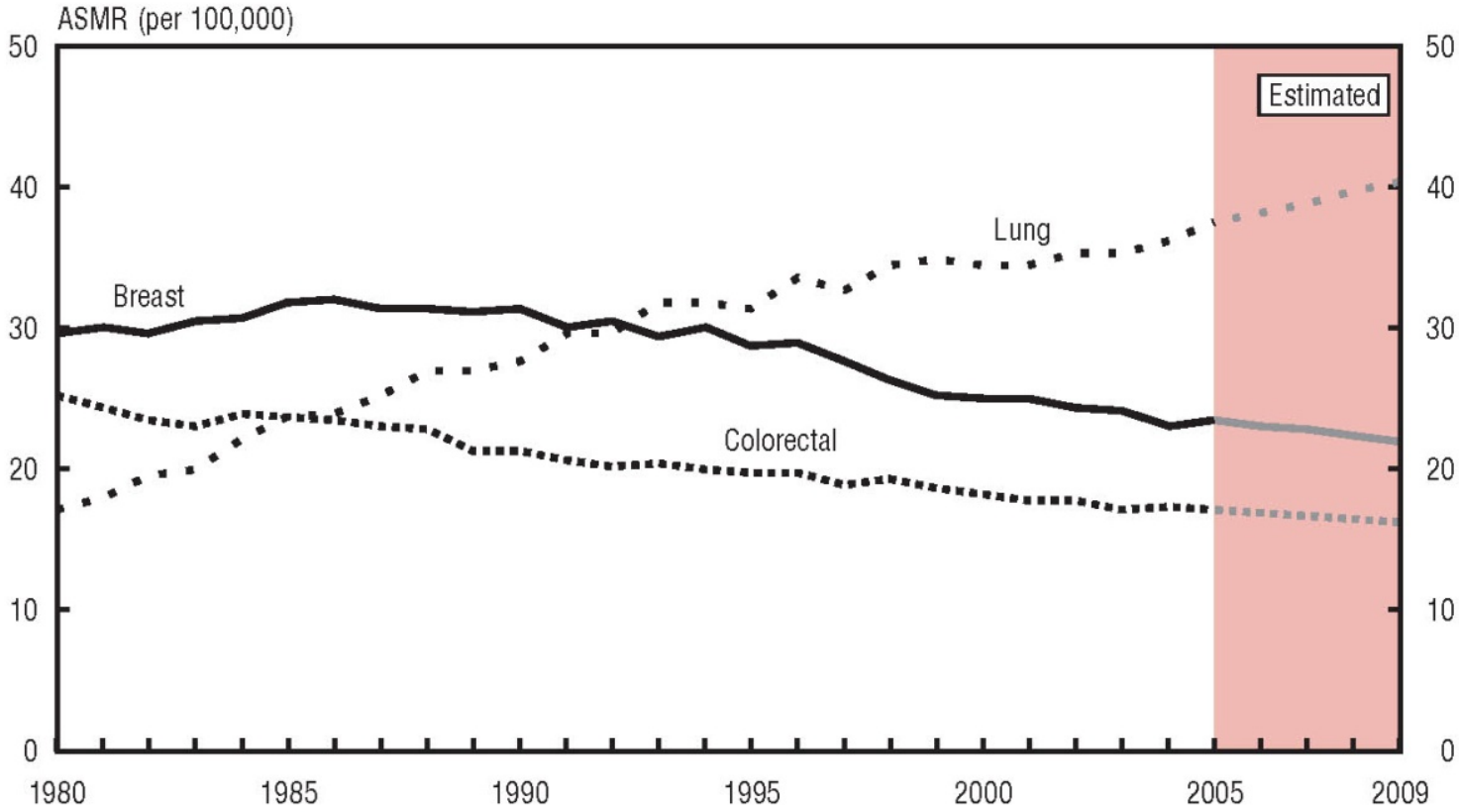
Mortality rates by province, per 100,000, women
2009 Canadian Cancer Society estimates

	Can	NL	PEI	NS	NB	Que	ON	Man	Sask	Alta	BC
All	147	152	154	169	151	155	145	155	146	143	133
Lung	40	42	41	41	35	49	38	37	33	33	38
Brst	22	27	25	25	21	23	22	25	21	21	19
Brst 2004	24	27	28	29	26	25	25	26	22	23	21

BC: the place to be!

Figure 4.9

Age-Standardized Mortality Rates (ASMR) for Selected Cancers, Females, Canada, 1980-2009



Note: Rates are age-standardized to the 1991 Canadian population.
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Adjuvant hormones therapy: then and now

Ancient history (when I started on staff in 1997)… to present-day adjuvant practice in BCCA

- **Then:**
- **Adjuvant chemo and hormone therapy**
  - Offered to T2 or greater disease stage if ER/PR+

- **Now:**
  - Hormone therapy to <u>any</u> ER+ ca, incl DCIS
  - Chemo to any T1c or higher, especially if grade 3
  - Trastuzumab, with chemo, to any T1b or higher

- **Why?**
  - Because we can….
  - …safely!

Flavours of Hormone Therapy

Tamoxifen

- Competes for estrogen receptor
- A weak estrogen in some tissues (bone, uterus, blood vessel)
- EBCCTG: 40% decrease in relapse, 33% decrease in mortality

Ovarian ablation (surgical or chemical):

- for pre-menopausal patients, if problems with Tam, or occasionally in addition to Tam

Aromatase Inhibitors (Anastrozole, Letrozole, Exemestane)

- Block the enzyme which makes estrogen outside of ovary
- Only effective in postmenopausal women

Trials of adjuvant aromatase inhibitors (AIs)

- **Conducted because of:**
  - Late relapses continuously arising after 5 years of tamoxifen
  - Lack of benefit to > 5 years tamoxifen
  - Slight superiority of AI's in metastatic setting, compared to tamoxifen

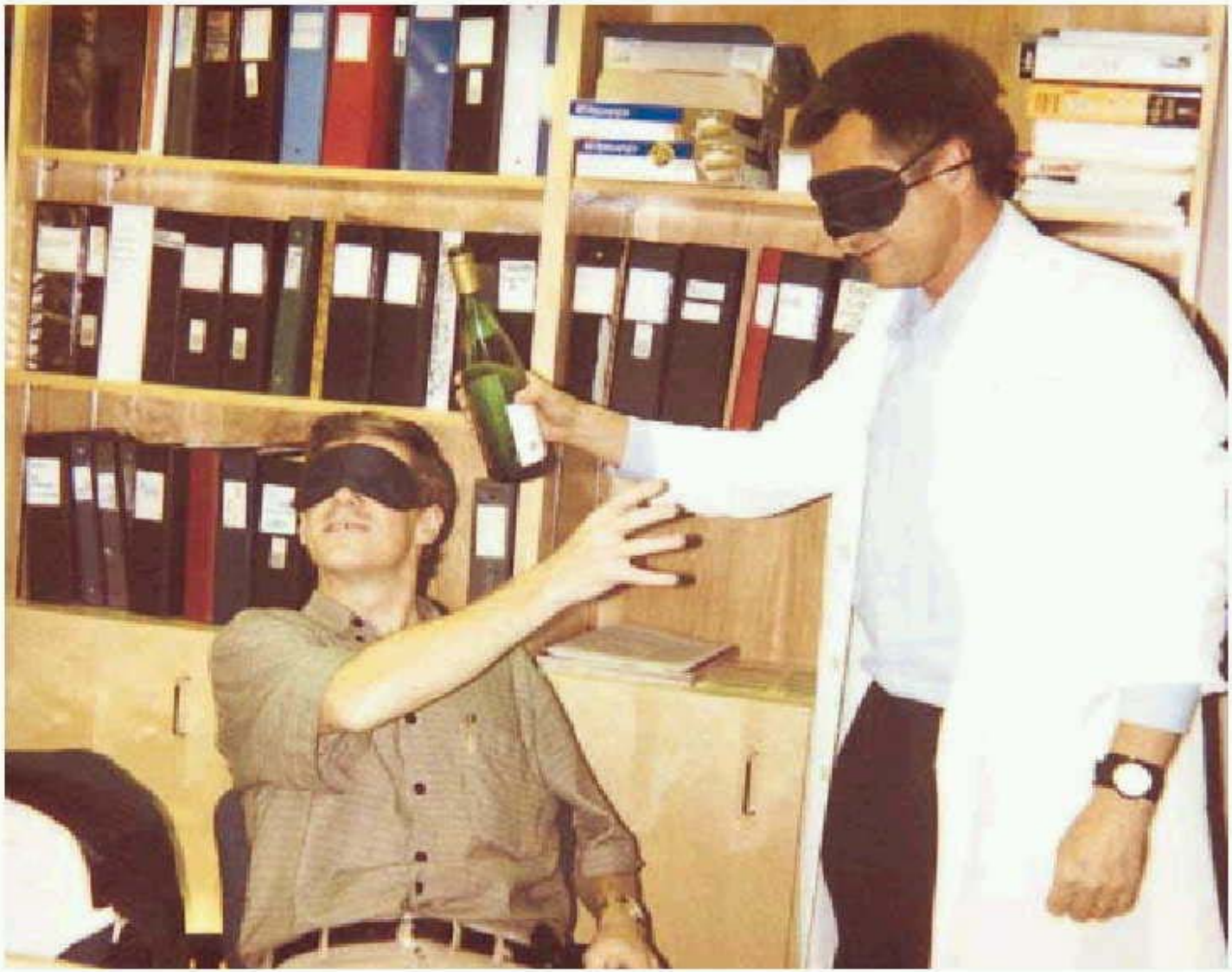
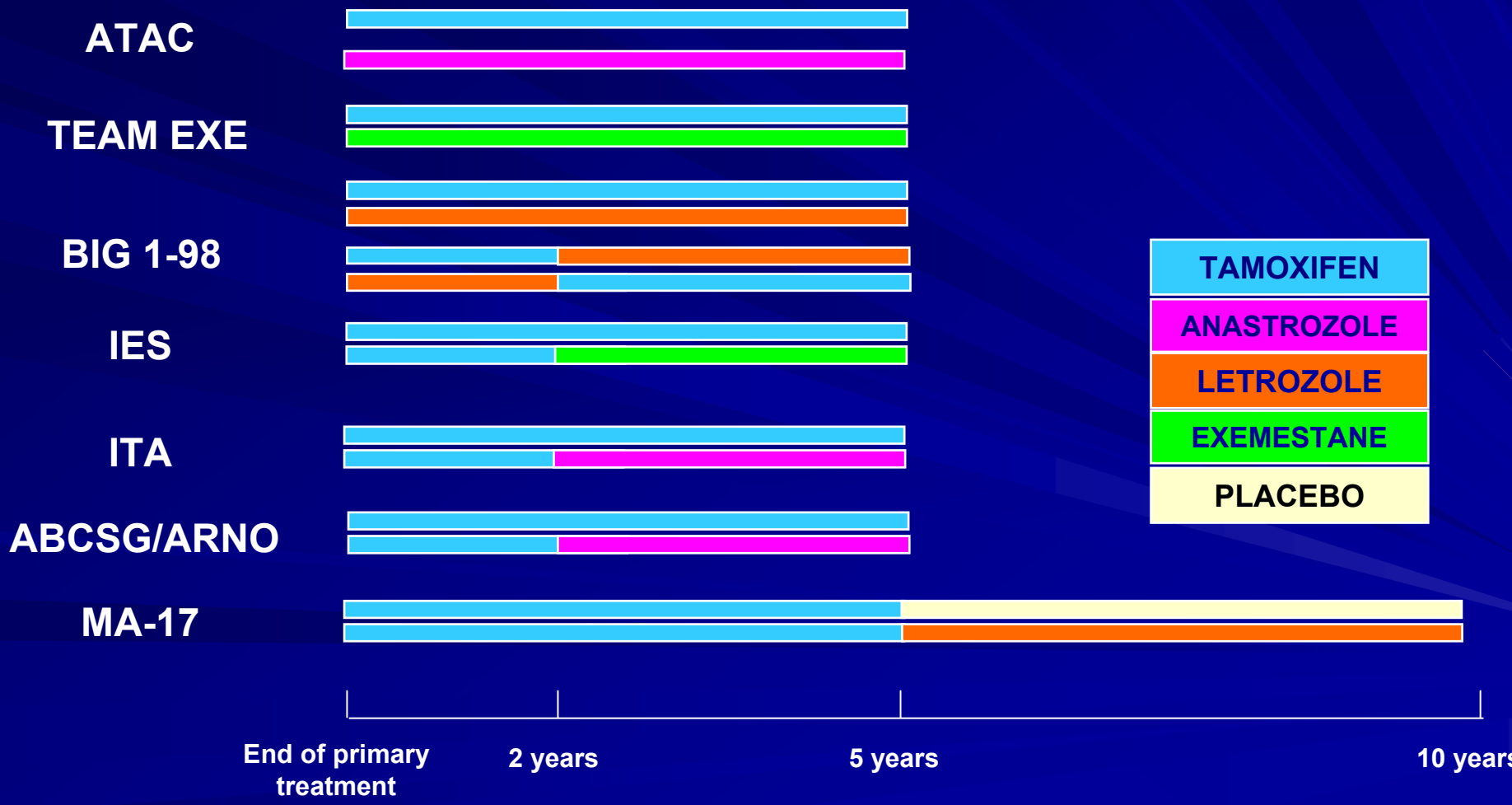


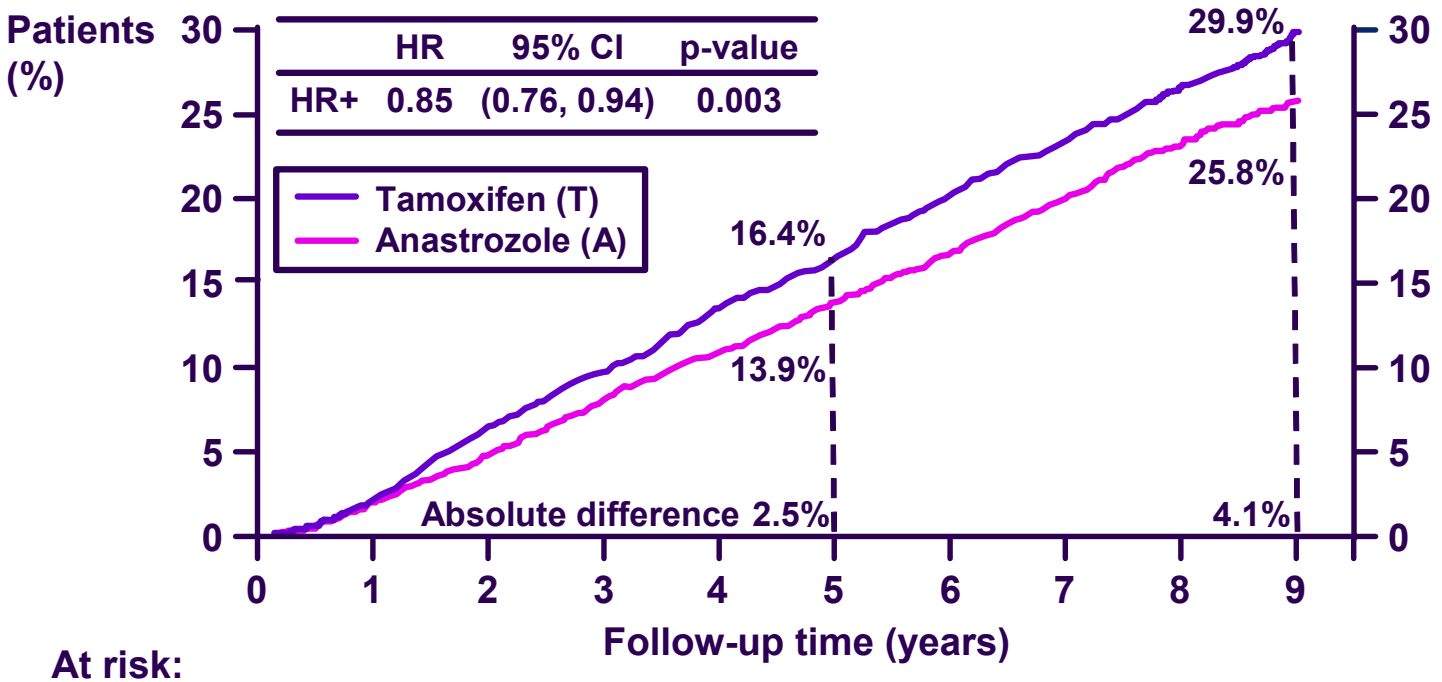
Fig. 1: The double-blind nature of the study was maintained throughout the trial. Dr. Innes is shown sitting.

AI Adjuvant Trial Strategies



Upfront AI: 8+ year results of ATAC:

Disease-free survival
HR+ patients



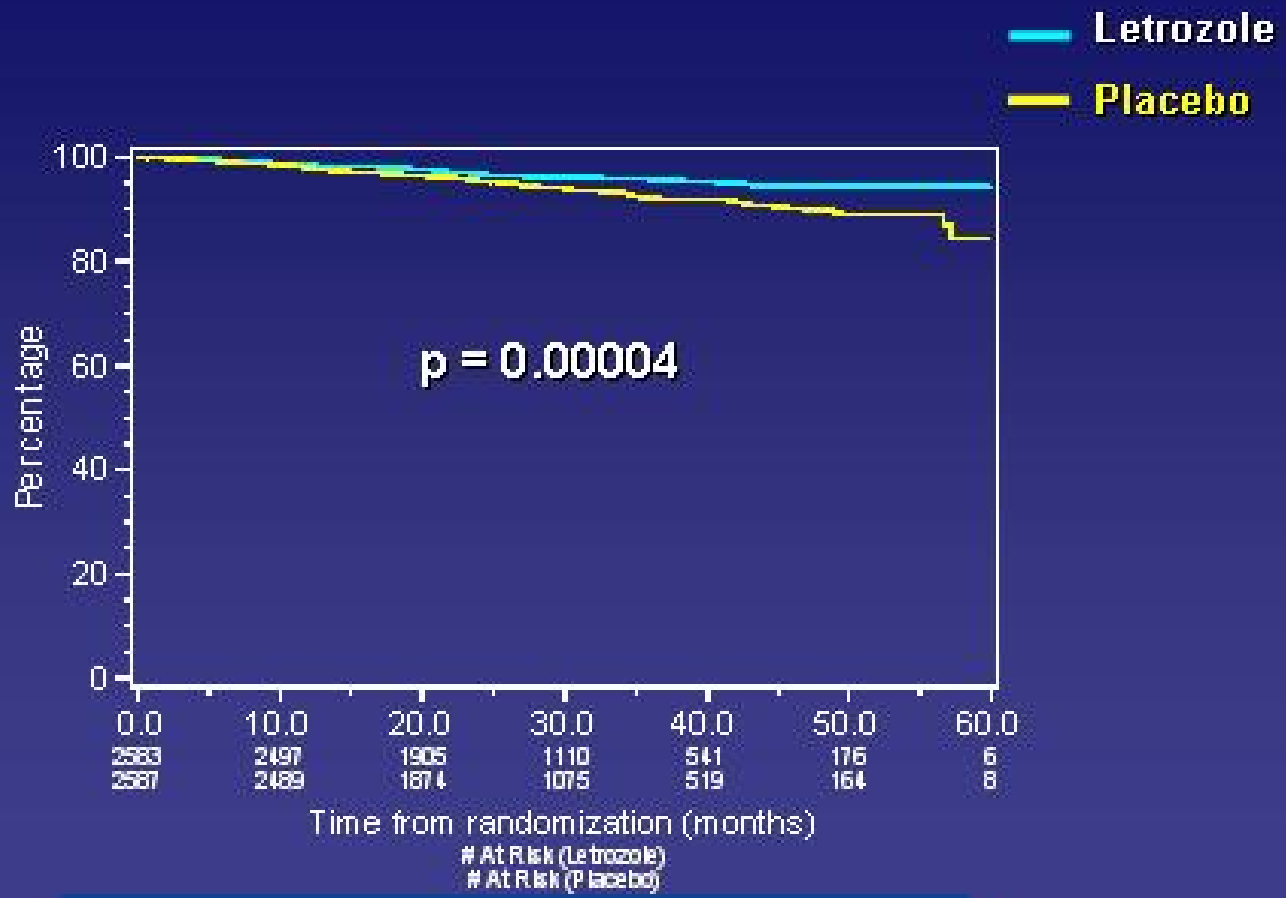
At risk:

A	2618	2541	2453	2361	2278	2159	1995	1801	1492	608
T	2598	2516	2400	2306	2196	2075	1896	1711	1396	547

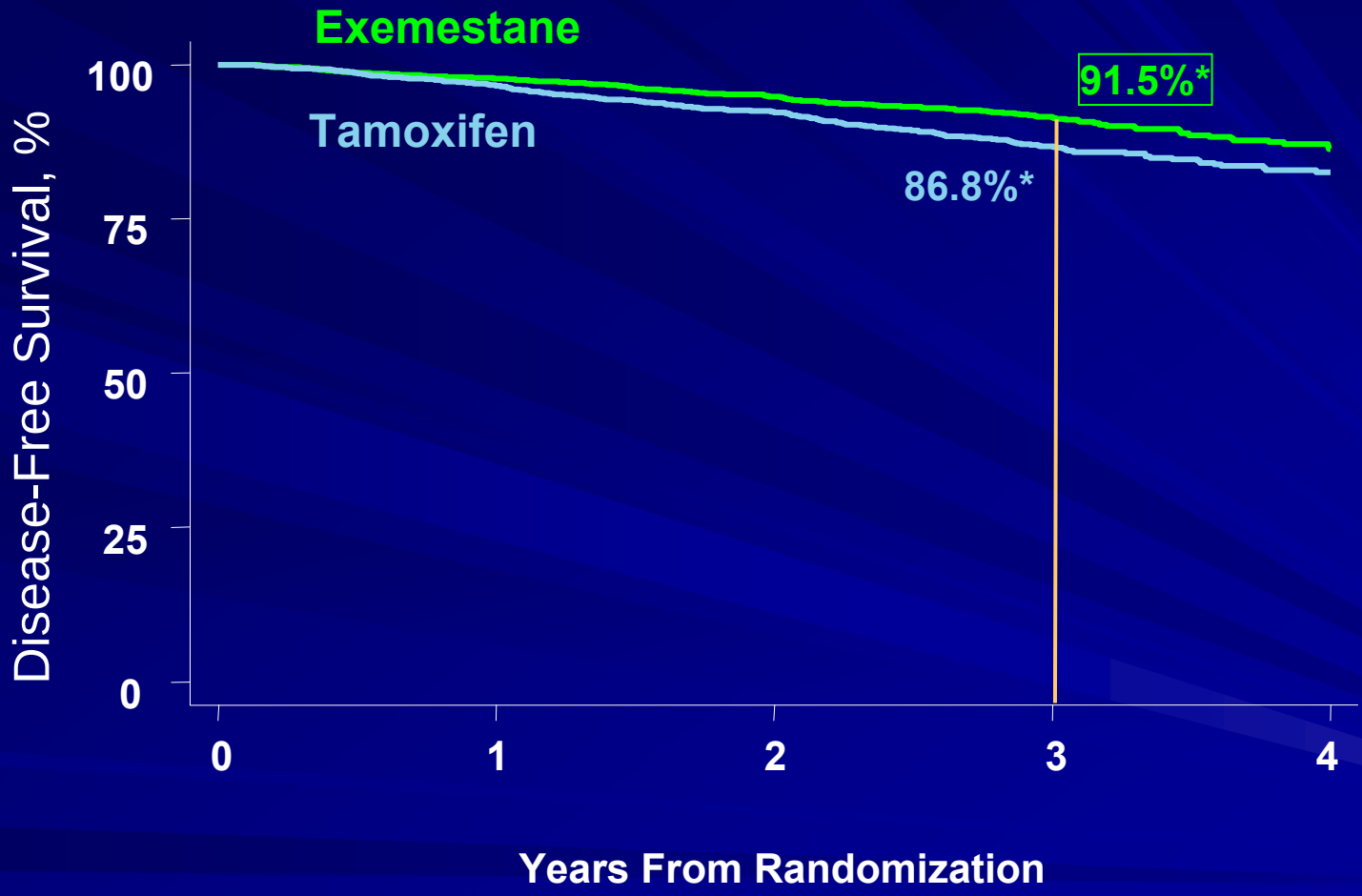
HR, hazard ratio; CI, confidence interval

NCIC MA17

Disease Free Survival – All Patients



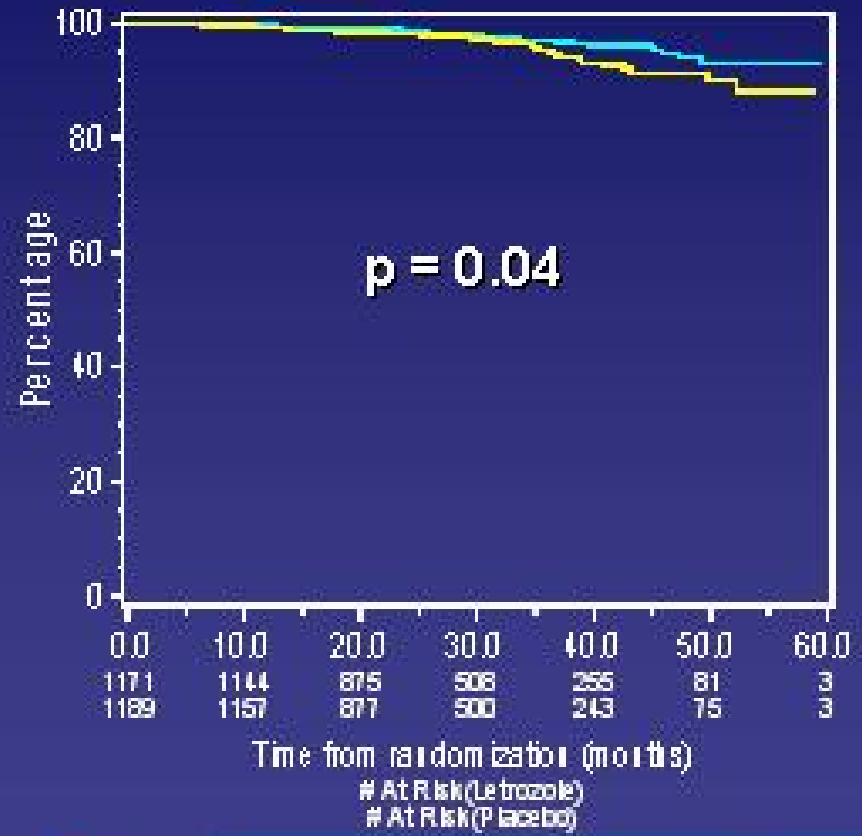
IES Trial: Disease-Free Survival



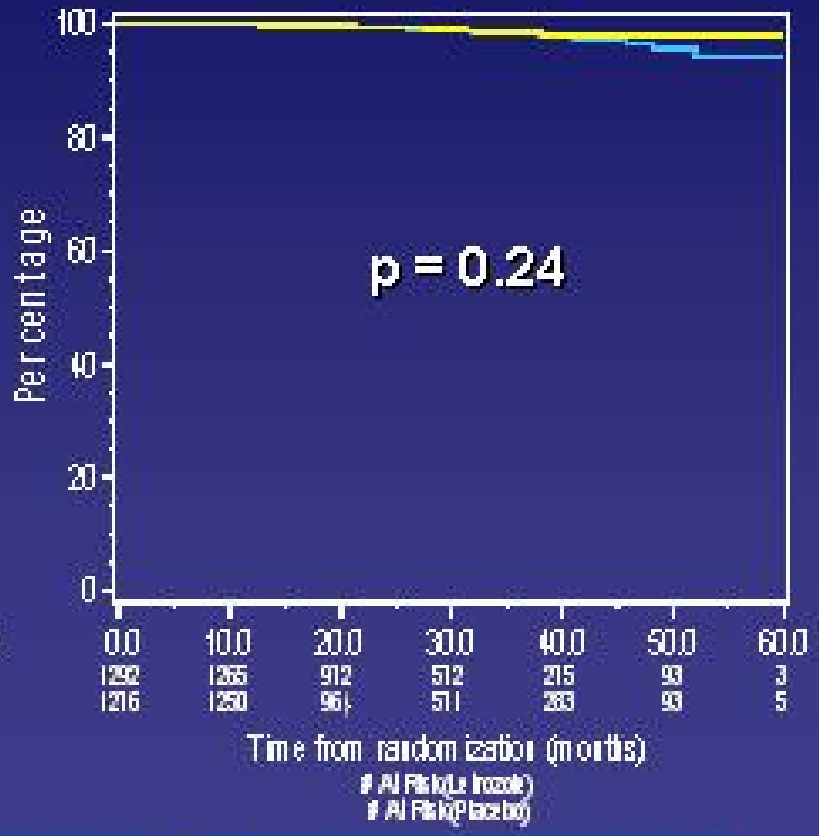
*Absolute difference at 36 months = 4.77. **Hazard ratio = 0.68** (95% CI: 0.56–0.82)
Log-rank test: *P = 0.00005.*

Overall Survival

Node Positive



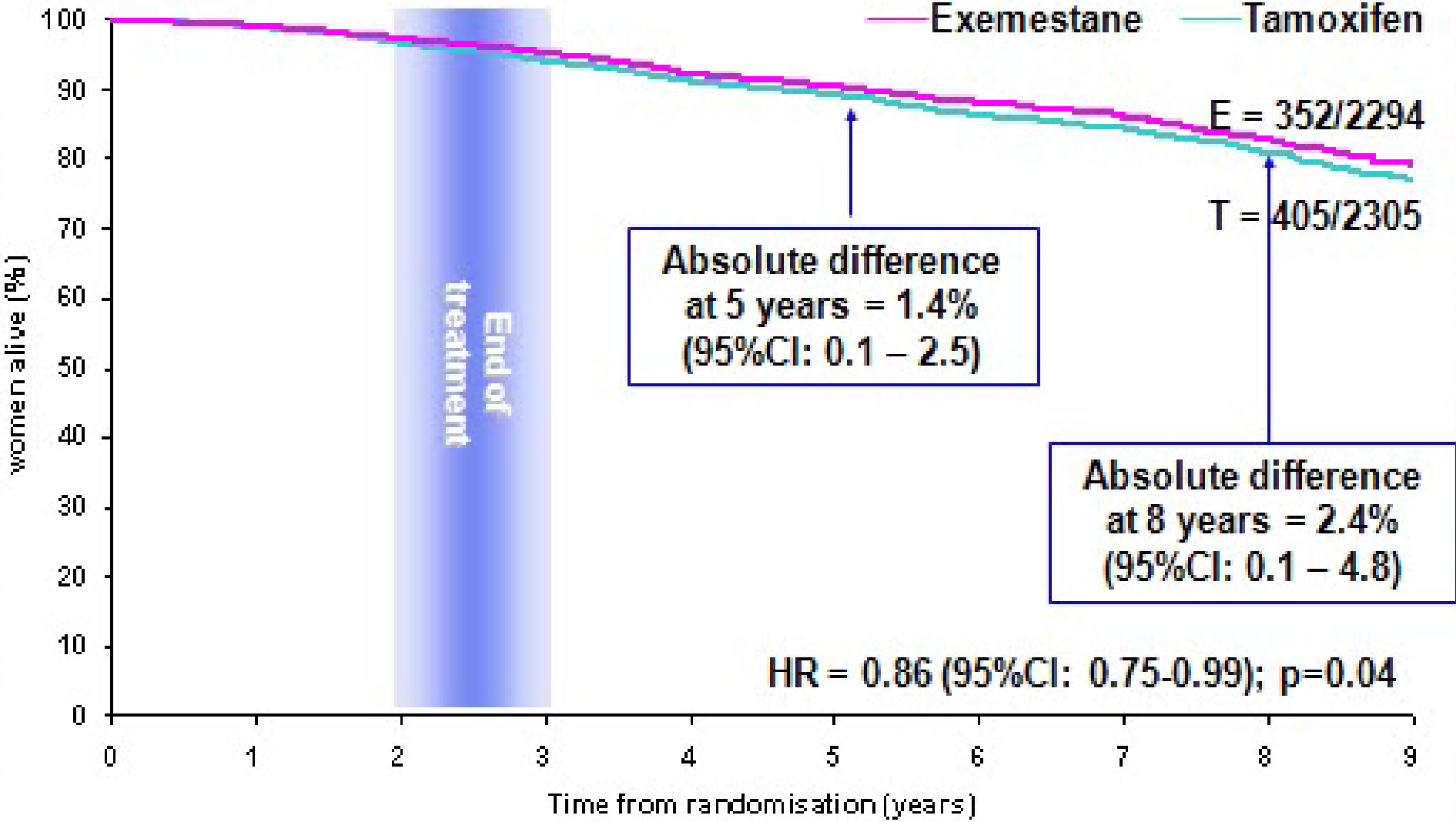
Node Negative



Letrozole

Placebo

Overall survival – ER+/unknown



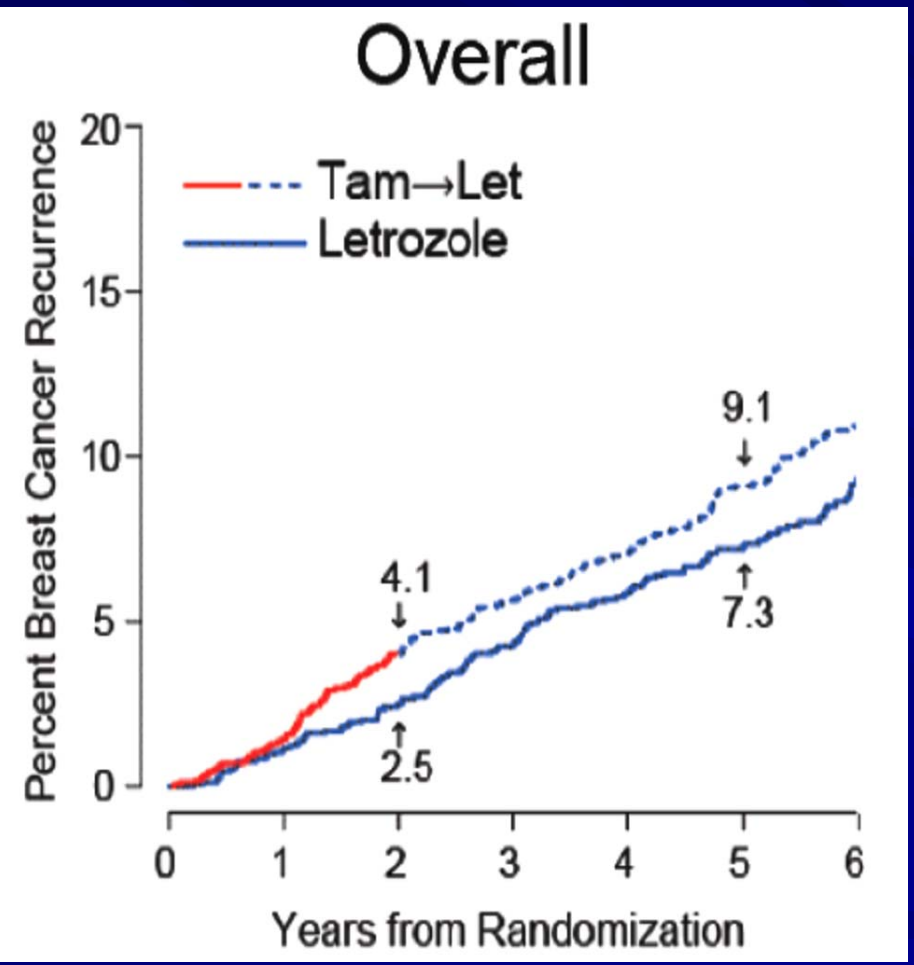
Number of events/at risk

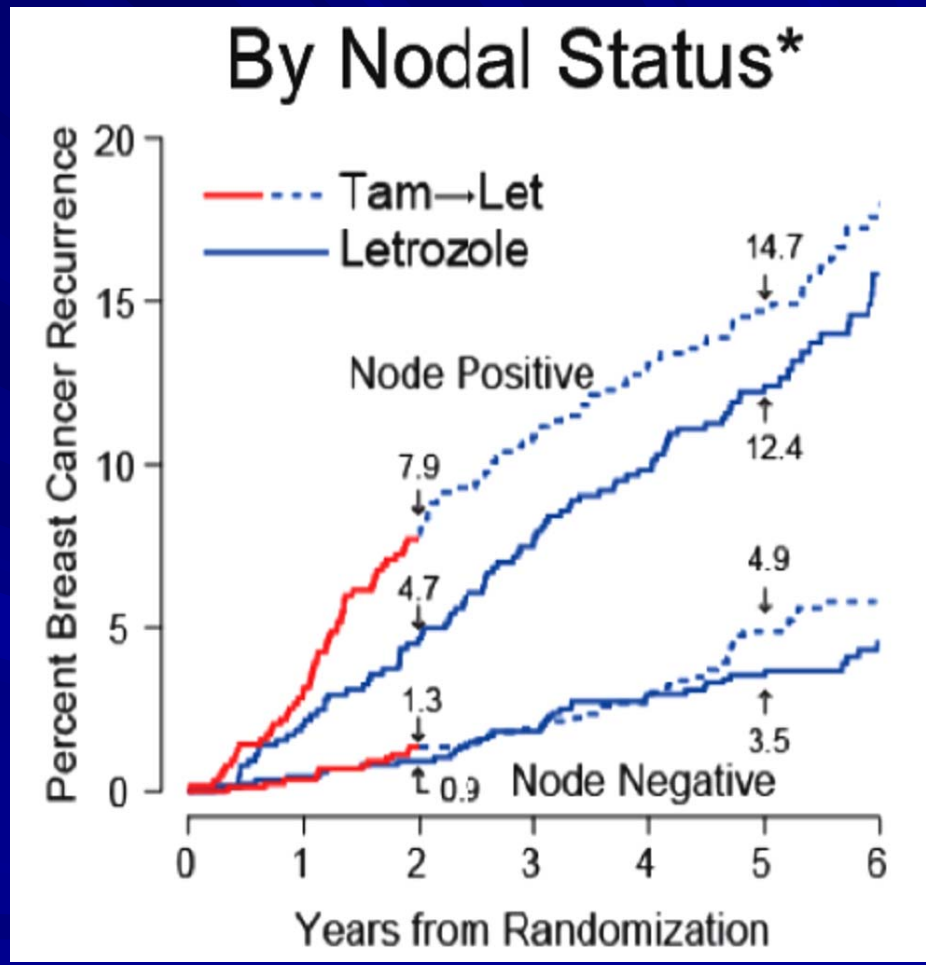
E	0/2294	17/2229	40/2177	42/2105	83/2008	38/1928	47/1781	42/1434	33/821	22+6*/291
T	0/2305	23/2249	52/2181	53/2094	83/1998	42/1912	81/1787	33/1411	44/787	23+6*/294

Caution: Incomparable trials!

- Different patient populations exist at 0, 2.5 and 5 yr entry timepoints
- Exception: BIG 1-98 trial

BIG 1-98 Trial: Recurrence after Upfront AI vs Sequence





42% Node positives

Side effect and risk differences: Tam vs AI

- How it feels: hot flashes, vaginal dryness, sleep change, weight change, transient nausea, achiness
- How they compare:
  - Tamoxifen: ? more hot flashes
  - AI: ? more achiness
- What patients risk:
  - **Tam:** slight increase in risk of blood clot, endometrial bleeding, thickening, rarely cancer; ?stroke
  - **AI:** increased risk for bone thinning, bone fracture; mild rises in lipids, ?CV risks

Bone risks of AI's in adjuvant trials

Bone density at baseline	Incidence of osteoporosis after 5 yrs anastrazole
Normal	0%
Osteopenia	15%

Bone density substudy from ATAC, ASCO 2006

- Remember, BMD ≠ fracture
- Some reversibility

Adjuvant hormone therapy trials

- **Findings across trials:**
  - AI-containing regimen reduced relapse risk compared to tamoxifen alone
- **Remaining questions:**
  - Does everyone need an AI?
  - Which strategy is best?
  - Which drug is best?
- **Answers unknown, but a policy necessary…**

Low risk breast cancer: between year 6 and 10 after diagnosis if free of cancer after 5 yrs of tamoxifen.

(BCCA data)

Pathologic TMN stage	N	Risk Of Breast Cancer Death	Risk Of Breast Cancer Occurrence (same or new)
Node negative	418	4%	10%
1-3 nodes positive	380	9	15
4-9 nodes positive	109	22	30
≤ 2cm Tumor	561	5	12
2-5 cm Tumor	392	12	19
T1 N0 Grade 1	42	0	3

High risk for relapse within 2.5 years on tamoxifen: BCCA data

	N	2.5 yr relapse rate(%) (95% CI)	P value
Grade			
I	544	1.1 (0.5-2.5)	< 0.001
II	2135	5.3 (4.4-6.4)	
III	1242	13.4 (11.6-15.5)	
ER status			
Mod/Hi >50fmol/mg	2990	6.5 (5.6-7.4)	0.005
Low 10-50 fmol/mg	393	14.5 (11.4-18.4)	
Node status			
0	1962	3.7 (2.9-4.6)	< 0.001
1-3	1650	8.5 (7.3-10)	
≥4	543	18.2 (14.3-20.7)	

BCCA policy for postmenopausal women

- Tamoxifen x 5 yrs for low risk disease
  - T1, N0, low grade, no LVI
- Upfront AI x 5 yrs for high risk disease
  - Stage 3 &/or grade 3 &/or weak ER+
- Tam for 2.5 yrs then AI for 2.5 years for all the rest
- If premenopausal for >3yrs tam, late switch
- Any AI
- Consider: BMD at baseline and then q2yrs if osteopenic, esp if on > 2-3 yrs therapy
  - Ca 1500 mg, Vit D 1000 IU daily

Cost considerations

- Tamoxifen $180 per 5 years
- AI $150 per month = $1800 per 1 year
- cost ↑ 50 x for upfront AI x 5 years

Surgical precision

- **Impact of nodal staging:**
  - Probably very little impact on adjuvant hormone use
  - More impact on use of chemo or not, type of chemo, amount of chemo, radiation or not (to nodes)

- **Clinical trials**
  - Currently treat N0 (i+) as N0, not requiring further node dissection
  - N1mic as N1, requiring nodal dissection

AI vs tam therapy & risk of 2nd primary Br Ca

- P1 Prevention trial in high risk women (tam v placebo):
  - Tam reduces BrCa risk by ~50%

- ATAC: 20 v 35 pts
- BIG: 0.4% v 0.7% of patients
- MA17: 14 v 26 pts
- IES: 20 v 35 pts

- MA.P3 trial: Exemestane v placebo:
  - underway at CSI and VC—hurry, it's not too late to refer!!!

MA.P3 prevention trial for postmenopausal high risk women

- **Eligible:**
  - Healthy postmenopausal woman > 60
  - Or <60 plus Gail score > 1.66
  - Or DCIS treated with mastectomy only
  - Or LCIS or atypical hyperplasia on any prior biopsy
- **Gail Score:**
  - Gail score > 1.66 in almost any postmenopausal woman with a 1st degree relative with Br Ca

Is there anyone who doesn't receive adjuvant therapy?

- **If ER+: if fit, all *offered* hormone adj tx**
  - Exception: mastectomy for DCIS
    - eligible for MA.P3 study
  - Partial mastectomy for DCIS
    - many will decline tamoxifen; AI not funded
  - T1N0 and higher
    - Depends on patient preference and estimated risk v benefit
- **Triple negative, T1a or b, or chemo-unfit may not have chemotherapy**
- **HER2+: T1b and higher: low threshold**

The things we know we don't know:

- **Is there a superior AI?**
  - Answer pending, MA27 study
- **Is more or longer therapy better?**
  - SOFT trial in premenopausal women
    - Combination better than tam?
  - NSABP B.42 and MA.17R
    - 8-10 yrs AI vs 5
- **Are other pathways important?**
  - MA33: Metformin v placebo
  - LISA: Impact of lifestyle changes in postmenopause
  - NSABP B43: Brief trastuzumab in HER2+ DCIS, B44?: sunitinib vs placebo in locally advanced, after non pCR
  - MAC.9: iv vs oral bisphosphonates

Summary

- Adjuvant hormone therapy: siege the day
- Spare no one! (almost)
- Tam alone vs AI regimens:
  - A small gain for a big number
- DCIS and primary prevention: AI's ahead?
- The road ahead: more siege engines?
- Less Mel?

It’s better in BC!!....especially in the Okanagan

Thank you for the invite